

WHAT IS CLAIMED IS:

1 1. A replicable genetic package displaying a compound other than an
2 expressed polypeptide, wherein the replicable genetic package comprises a heterologous
3 nucleic acid tag encoding a characteristic of the compound.

1 2. The replicable genetic package of claim 1, wherein the replicable
2 genetic package is selected from the group consisting of a virus, a bacteriophage, a bacterium
3 and a spore.

1 3. The replicable genetic package of claim 2, wherein the replicable
2 genetic package is a bacteriophage.

1 4. The replicable genetic package of claim 3, wherein the bacteriophage is
2 a filamentous phage.

1 5. The replicable genetic package of claim 3, wherein the bacteriophage is
2 a non-filamentous phage.

1 6. The replicable genetic package of claim 3, wherein the bacteriophage is
2 an icosahedral phage.

1 7. The replicable genetic package of claim 1, wherein the compound is a
2 small molecule.

1 8. The replicable genetic package of claim 1, wherein the compound
2 comprises a polypeptide linked to a small molecule.

1 9. The replicable genetic package of claim 1, wherein if the compound is
2 a peptide then the replicable genetic package and the compound are attached by other than a
3 peptide linkage.

1 10. The replicable genetic package of claim 1, wherein the replicable
2 genetic package and compound are joined via a covalent bond formed between an
3 endogenous functional group on the replicable genetic package and a functional group borne
4 by the compound.

1 11. The replicable genetic package of claim 1, wherein the replicable

genetic package bears a package linker and the compound is attached to the replicable genetic package by association with the package linker.

12. The replicable genetic package of claim 1, wherein the compound bears a compound linker and the compound is attached to the replicable genetic package via the compound linker.

13. The replicable genetic package of claim 1, wherein the replicable genetic package bears a package linker and the compound a compound linker and the compound is attached to the replicable genetic package by association of the linkers.

14. The replicable genetic package of claim 13, wherein the replicable genetic package and the compound are linked by a non-covalent interaction.

15. The replicable genetic package of claim 13, wherein the package linker and compound linker are members of a binding pair.

16. The replicable genetic package of claim 15, wherein binding pair members comprise a binding protein and a ligand having specific binding affinity for the binding protein.

17. The replicable genetic package of claim 16, wherein the binding protein is an antibody and the ligand is a hapten.

18. The replicable genetic package of claim 15, wherein the binding pair members comprise biotin and either avidin, streptavidin or neutravidin.

19. The replicable genetic package of claim 15, wherein the binding pair members comprise peptide dimerization domains.

20. The replicable genetic package of claim 13, further comprising a bridging linker that effects association of the package linker and the compound linker.

21. The replicable genetic package of claim 20, wherein at least one of the linkers is a reversible linker.

22. The replicable genetic package of claim 1, wherein the replicable genetic package displays a plurality of compounds.

23. The replicable genetic package of claim 22, wherein the replicable genetic package is a phage and the plurality of compounds are attached to different coat proteins having different sequences, and each of the different coat proteins bears one or more of the compounds.

24. The replicable genetic package of claim 23, wherein the plurality of compounds are the same.

25. The replicable genetic package of claim 24, wherein at least some of the plurality of compounds are different.

26. The replicable genetic package of claim 22, wherein the replicable genetic package is a phage and the plurality of compounds are attached to a plurality of coat proteins having the same sequence, and each of the plurality of coat proteins bears one or more of the compounds.

27. The replicable genetic package of claim 26, wherein the plurality of compounds are the same.

28. The replicable genetic package of claim 26, wherein at least some of the plurality of compounds are different.

29. The replicable genetic package of claim 22, wherein the plurality of compounds are attached to a single coat protein.

30. The replicable genetic package of claim 22, wherein the replicable genetic package is a phage and bears a plurality of exogenous attachment sites of the same type on a single coat protein or a plurality of coat proteins of the same sequence such that each of the coat proteins bear one or more of the attachment sites, and the plurality of compounds are associated with the replicable genetic package via the attachment sites.

31. The replicable genetic package of claim 22, wherein the replicable genetic package is a phage and bears a plurality of exogenous attachment sites of the same type on a plurality of coat proteins having different sequences such that each of the coat proteins bear one or more of the attachment sites, and the plurality of compounds are associated with the replicable genetic package via the attachment sites.

32. The replicable genetic package of claim 22, wherein the replicable genetic package is a phage and bears a plurality of exogenous attachment sites of different types on a single coat protein or a plurality of coat proteins of the same sequence such that each of the coat proteins bear one or more of the attachment sites, and the plurality of compounds are associated with the replicable genetic package via the attachment sites.

33. The replicable genetic package of claim 22, wherein the replicable genetic package is a phage and bears a plurality of exogenous attachment sites of different types on a plurality of coat proteins having different sequences such that each of the coat proteins bear one or more of the attachment sites, and the plurality of compounds are associated with the replicable genetic package via the attachment sites.

34. The replicable genetic package of claim 1, wherein the heterologous nucleic acid tag is a nucleic acid segment other than a segment that encodes for a polypeptide displayed on the replicable genetic package.

35. The replicable genetic package of claim 1, wherein the heterologous nucleic acid tag encodes the identity of the compound.

36. The replicable genetic package of claim 1, wherein the heterologous nucleic acid tag encodes a value or symbol assigned to the compound.

37. The replicable genetic package of claim 1, wherein

(a) the replicable genetic package is a phage; and

(b) the heterologous nucleic acid tag is inserted into a segment of the genome of the phage such that it is flanked by a heterologous promoter and a heterologous restriction site, the heterologous promoter being in operable linkage with the heterologous nucleic acid tag.

38. The replicable genetic package of claim 37, wherein the heterologous promoter is selected from the group consisting of a phage T7 promoter, a T3 promoter and a sp6 promoter.

39. The replicable genetic package of claim 1, wherein the replicable genetic package comprises a collection of replicable genetic packages, each replicable genetic

3 package bearing a different compound and harboring a different heterologous nucleic acid
4 tag.

1 40. The replicable genetic package of claim 39, wherein each of the
2 heterologous nucleic acid tags from the different replicable genetic package are isothermal
3 tags.

1 41. The replicable genetic package of claim 39, wherein the replicable
2 genetic packages are bacteriophage.

1 42. The replicable genetic package of claim 39, wherein each replicable
2 genetic package bears a different compound from a combinatorial library of small molecules.

1 43. The replicable genetic package of claim 39, wherein at least a plurality
2 of the replicable genetic packages are directly attached to the compound by a covalent bond
3 formed from an endogenous functional group on the replicable genetic package and a
4 functional group borne by the compound.

1 44. The replicable genetic package of claim 39, wherein at least a plurality
2 of the replicable genetic packages are attached to the compound via one or more linkers.

1 45. A replicable genetic package displaying a compound other than an
2 expressed polypeptide, wherein the replicable genetic package and the compound are attached
3 via a linker.

1 46. The replicable genetic package of claim 45, wherein the replicable
2 genetic package is a collection of replicable genetic packages, each replicable genetic package
3 in the collection bearing a different compound.

1 47. The replicable genetic package of claim 45, wherein the compound is a
2 small molecule.

1 48. The replicable genetic package of claim 45, wherein the replicable
2 genetic package is a bacteriophage.

1 49. The replicable genetic package of claim 45, wherein the linker is a
2 package linker attached to the replicable genetic package and the compound is attached to the
3 replicable genetic package via the package linker.

1 50. The replicable genetic package of claim 45, wherein the linker is a
2 compound linker borne by the compound and the replicable genetic package is attached to the
3 compound via the compound linker.

1 51. The replicable genetic package of claim 45, wherein the linker is a
2 package linker borne by the replicable genetic package, and the compound bears a compound
3 linker and the compound is attached to the replicable genetic package by association of the
4 package and compound linkers.

1 52. The replicable genetic package of claim 51, wherein the replicable
2 genetic package and the compound are attached via a non-covalent interaction between
3 package and compound linkers.

1 53. The replicable genetic package of claim 51, wherein the replicable
2 genetic package and the compound are attached via a covalent bond formed between package
3 and compound linkers.

1 54. The replicable genetic package of claim 45, wherein the replicable
2 genetic package displays a plurality of compounds.

1 55. A replicable genetic package displaying a compound, wherein the
2 replicable genetic package comprises a heterologous nucleic acid tag encoding a
3 characteristic of the compound by a code other than the standard genetic code.

1 56. The replicable genetic package of claim 55, wherein the replicable
2 genetic package displays a plurality of compounds.

1 57. The replicable genetic package of claim 56, wherein at least some of
2 the plurality of compounds are different.

1 58. The replicable genetic package of claim 55, wherein the replicable
2 genetic package is a bacteriophage.

1 59. The replicable genetic package of claim 55, wherein the compound is a
2 small molecule.

1 60. The replicable genetic package of claim 55, wherein the replicable

2 genetic package is a collection of replicable genetic packages, each replicable genetic package
3 in the collection bearing a different compound from a combinatorial library.

1 61. A method of screening a library of compounds, comprising:

2 (a) providing a plurality of replicable genetic packages displaying different
3 compounds, wherein the compounds are other than an expressed polypeptide; and

4 (b) assaying the replicable genetic packages to identify at least one
5 replicable genetic package displaying at least one compound with a desired property.

1 62. The method of claim 61, wherein the replicable genetic package is
2 selected from the group consisting of a virus, a bacteriophage, a bacterium and a spore.

1 63. The method of claim 62, wherein the replicable genetic package is a
2 bacteriophage.

1 64. The method of claim 61, further comprising for each compound to be
2 screened, contacting the compound with a replicable genetic package to form the plurality of
3 replicable genetic packages displaying different compounds.

1 65. The method of claim 64, wherein at least one of the replicable genetic
2 packages becomes attached to one of the compounds during the contacting step via a covalent
3 bond formed between an endogenous functional group on the at least one replicable genetic
4 package and a functional group borne by the compounds.

1 66. The method of claim 64, wherein at least one of the replicable genetic
2 packages becomes attached to one of the compounds during the contacting step via a
3 modified endogenous functional group borne by the at least one replicable genetic package.

1 67. The method of claim 64, further comprising modifying an endogenous
2 functional group borne by one or more of the plurality of replicable genetic packages prior to
3 the contacting step.

1 68. The method of claim 67, wherein modifying comprises chemically
2 modifying an endogenous amino acid or polypeptide at a surface of the one or more
3 replicable genetic packages.

1 69. The method of claim 67, wherein modifying comprises enzymatically-

modifying an endogenous amino acid or polypeptide at a surface of the one or more replicable genetic packages.

70. The method of claim 64, wherein one or more of the replicable genetic packages bears a package linker and the compound becomes attached to the one or more replicable genetic packages by association with the package linker during the contacting stage.

71. The method of claim 64, wherein one or more of the compounds bear a compound linker and the compound becomes attached to the replicable genetic package via the compound linker during the contacting stage.

72. The method of claim 64, wherein one or more of the replicable genetic packages bears a package linker and one or more of the compounds bears a compound linker and the one or more compounds and the one or more replicable genetic packages become attached via the association between the linkers during the contacting step.

73. The method of claim 72, wherein the package and compound linker are members of a binding pair.

74. The method of claim 64, further comprising immobilizing replicable genetic packages to a support, and wherein contacting comprises contacting the immobilized replicable genetic packages with the compounds to form the plurality of replicable genetic packages.

75. The method of claim 74, wherein the replicable genetic packages are immobilized to the support via a reversible linker and the method further comprises cleaving the plurality of replicable genetic packages from the support.

76. The method of claim 75, wherein the reversible linker comprises photocleavable-biotin.

77. The method of claim 64, wherein the compounds to be screened are combined into a plurality of pools and each pool is contacted with a single type of replicable genetic package.

78. The method of claim 64, wherein replicable genetic packages are

combined into a plurality of pools and each pool is contacted with a single type of compound.

79. The method of claim 64, wherein the replicable genetic packages are combined into a plurality of pools and each pool is contacted with a plurality of compounds.

80. The method of claim 64, wherein the replicable genetic packages are phage and one or more of the replicable genetic packages bear a plurality of attachment sites of the same type on a single coat protein or a plurality of coat proteins of the same sequence such that each of the coat proteins bear one or more attachment sites, and contacting comprises contacting the one or more replicable genetic packages with a plurality of compounds, the compounds attaching to the attachment sites to form the one or more replicable genetic packages displaying multiple different compounds.

81. The method of claim 64, wherein the replicable genetic packages are phage and one or more of the replicable genetic packages bear a plurality of attachment sites of the same type on a plurality of coat proteins having different sequences such that each of the coat proteins bear one or more attachment sites, and contacting comprises contacting the one or more replicable genetic packages with a plurality of compounds, the compounds attaching to the attachment sites to form the one or more replicable genetic packages displaying multiple different compounds.

82. The method of claim 64, wherein the replicable genetic packages are phage and one or more of the replicable genetic packages bear a plurality of different attachment sites on a single coat protein or a plurality of coat proteins of the same sequence such that each of the coat proteins bear one or more attachment sites, and contacting comprises contacting the one or more replicable genetic packages with a plurality of compounds, the compounds attaching to the attachment sites to form the one or more replicable genetic packages displaying multiple different compounds.

83. The method of claim 64, wherein the replicable genetic packages are phage and one or more of the replicable genetic packages bear a plurality of different attachment sites on a plurality of coat proteins having different sequences such that each of the coat proteins bear one or more attachment sites, and contacting comprises contacting the one or more replicable genetic packages with a plurality of compounds, the compounds attaching to the attachment sites to form the one or more replicable genetic packages displaying multiple different compounds.

84. The method of claim 80, wherein the one or more replicable genetic packages are bacteriophage and the different attachment sites are located on different coat proteins of the bacteriophage.

85. The method of claim 80, wherein the one or more replicable genetic packages are bacteriophage and the different attachment sites are located on the same coat proteins of the bacteriophage.

86. The method of claim 64, wherein contacting comprises separately contacting different compounds with the replicable genetic packages such that the plurality of replicable genetic compounds each display only a single type of compound, and assaying comprises separately assaying the plurality of replicable genetic packages.

87. The method of claim 61, further comprises determining at least one characteristic of the at least one compound with the desired property.

88. The method of claim 61, wherein the desired property is the interaction of multiple compounds borne by a replicable genetic package with a target molecule and assaying comprises contacting the plurality of replicable genetic packages with the target and identifying at least one replicable genetic package displaying multiple compounds that interact with the target molecule.

89. The method of claim 61, wherein the desired property is selected from the group consisting of the capacity to bind to a receptor, the capacity to be transported into or through a cell, the capacity to be a substrate or inhibitor for an enzyme, the capacity to kill bacteria, fungi or other microorganisms, and the capacity to agonize or antagonize a receptor.

90. The method of claim 89, wherein the desired property is capacity to bind a receptor and the assaying step comprises contacting the plurality of replicable genetic packages with the receptor and identifying at least one replicable genetic package displaying a compound that binds to the receptor.

91. The method of claim 89, wherein the desired property is capacity to bind at least one of several receptors, and the assaying step comprises contacting the plurality of replicable genetic packages with a plurality of receptors of different types and identifying at least one replicable genetic package displaying a compound that binds to one of the

5 receptors.

1 92. The method of claim 91, wherein the different receptors are
2 immobilized on supports, different receptors being attached to different supports that each
3 have a distinctive characteristic.

1 93. The method of claim 92, further comprising determining the
2 characteristic of at least one of the supports bearing a receptor bound to one of the replicable
3 genetic packages, the characteristic providing an indication of the identity of the receptor to
4 which one of the replicable genetic packages is bound.

1 94. The method of claim 89, wherein the desired property is the capacity to
2 be transported into or through a cell and the assaying step comprises contacting the plurality
3 of replicable genetic packages with the cell and identifying at least one replicable genetic
4 package displaying a compound that is transported into or through the cell.

1 95. The method of claim 94, wherein the contacting step is performed in
2 vitro.

1 96. The method of claim 95, wherein the cell is a population of polarized
2 cells arranged in a monolayer.

1 97. The method of claim 96, wherein the monolayer is layered above a
2 membrane that is impermeable to the plurality of replicable genetic packages and assaying
3 comprises detecting transport of the at least one replicable genetic package through the cell to
4 the membrane.

1 98. The method of claim 94, wherein the contacting step is performed in
2 vivo.

1 99. The method of claim 98, wherein

2 (a) the contacting step comprises introducing the plurality of replicable
3 genetic packages into a body compartment or tissue of an animal;

4 (b) the cell is a plurality of cells lining the body compartment or tissue;
5 and

6 (c) the identifying step comprises retrieving the at least one of the plurality
7 of replicable genetic packages from a tissue or fluid after being transported through the cells
8 lining the cavity.

1 100. The method of claim 99, wherein the plurality of replicable genetic
2 packages are introduced into the intestine of the animal, the cells through which transport
3 occurs are intestinal epithelial cells and the at least one replicable genetic package is retrieved
4 from the blood.

1 101. The method of claim 99, wherein the plurality of replicable genetic
2 packages are introduced into the circulatory system of the animal, the cells through which
3 transport occurs are endothelial cells and the at least one replicable genetic package is
4 retrieved from the brain.

1 102. The method of claim 89, wherein the desired property is capacity to be
2 a substrate or inhibitor of an enzyme and the assaying step comprises contacting the plurality
3 of replicable genetic packages with the enzyme and identifying at least one replicable genetic
4 package displaying a compound that is a substrate or an inhibitor of the enzyme.

1 103. The method of claim 102, wherein the desired property is capacity to
2 be a substrate of an enzyme and identifying comprises detecting absence of compound from
3 the at least one replicable genetic package.

1 104. The method of claim 102, wherein the desired property is capacity to
2 be a substrate of an enzyme and identifying comprises detecting the absence of an indicator
3 from the at least one replicable genetic package.

1 105. The method of claim 104, wherein the indicator is an epitope that is
2 released by action of the enzyme on the compound borne by the at least one replicable genetic
3 package.

1 106. The method of claim 102, wherein the desired property is capacity to
2 be a substrate of an enzyme and identifying comprises detecting presence of an enzymatic
3 product borne by the at least one replicable genetic package.

1 107. A method of screening a library of compounds, comprising:

2 (a) providing a plurality of different replicable genetic packages each
3 displaying a compound other than an expressed polypeptide, different replicable genetic
4 packages displaying different compounds and harboring different heterologous nucleic acid
5 tags;

6 (b) assaying the plurality of replicable genetic packages to identify at least
7 one replicable genetic package displaying at least one compound with a desired property; and

8 (c) decoding the heterologous nucleic acid tag of the at least one replicable
9 genetic package to identify a characteristic of the at least one compound with the desirable
10 property.

1 108. The method of claim 107, wherein the nucleic acid tag is a nucleic acid
2 segment other than a segment that encodes for an expressed polypeptide displayed by the
3 replicable genetic package.

1 109. The method of claim 107, further comprising for each compound to be
2 screened, contacting the compound with a replicable genetic package, different compounds
3 being contacted with different replicable genetic packages, thereby forming the plurality of
4 different replicable genetic packages.

1 110. The method of claim 109, further comprising generating a
2 correspondence regime indicating which compound is attached to which replicable genetic
3 package.

1 111. The method of claim 110, wherein the correspondence regime is a
2 correspondence regime between compounds and the heterologous nucleic acid tags harbored
3 by the replicable genetic packages, and the characteristic of the at least one compound is
4 determined by matching the sequence of the heterologous nucleic acid tag of the at least one
5 replicable genetic package and a sequence of a heterologous nucleic acid tag in the
6 correspondence regime.

1 112. The method of claim 109, wherein each compound is contacted with
2 one or more replicable genetic packages that each harbor the same heterologous nucleic acid
3 tag, whereby each replicable genetic package bears a single type of compound and replicable
4 genetic packages harboring the same heterologous nucleic acid tags display the same
5 compound and replicable genetic packages harboring different heterologous nucleic acid tags
6 display different compounds.

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113. The method of claim 109, wherein

(a) the compounds to be screened are combined into a plurality of pools and each pool is contacted with one or more replicable genetic packages that harbor the same heterologous nucleic acid tag, whereby each of the plurality of replicable genetic packages display a plurality of different compounds; and

(b) assaying comprises

(i) assaying the plurality replicable genetic packages to identify an initial replicable genetic package displaying a plurality of compounds wherein at least one of the plurality of compounds has the desired activity; and

(ii) repeating the assay with a set of replicable genetic packages, wherein each member of the set displays one of the compounds borne by the initial replicable genetic package to identify the at least one replicable genetic package.

114. The method of claim 107, wherein the decoding step is performed by sequencing the heterologous nucleic acid tag of the at least one replicable genetic package.

115. The method of claim 107, wherein the decoding comprises:

(a) generating a nucleic acid probe from the at least one replicable genetic package, the nucleic acid probe comprising or being complementary to the heterologous nucleic acid tag of the at least one replicable genetic package; and

(b) contacting the probe to the heterologous nucleic acid tag from the different replicable genetic packages to identify the replicable genetic package to which the at least one compound was attached.

116. The method of claim 115, further comprising determining the identity of the at least one compound from a correspondence regime between different replicable genetic packages and different compounds.

117. The method of claim 115, wherein the replicable genetic packages are arranged in an array for the contacting step.

118. The method of claim 107, wherein the desired property is selected from the group consisting of the capacity to bind to a receptor, the capacity to be transported into or through a cell, the capacity to be a substrate or inhibitor for an enzyme, the capacity to kill

4 bacteria fungi or other microorganisms, and the capacity to agonize or antagonize a receptor.

1 119. The method of claim 118, wherein the desired property is capacity to
2 bind a receptor and the assaying step comprises contacting the replicable genetic packages
3 displaying different compounds with the receptor and identifying at least one replicable
4 genetic package displaying a compound that binds to the receptor.

1 120. The method of claim 118, wherein the desired property is the capacity
2 to be transported into or through a cell and the assaying step comprises contacting the
3 replicable genetic packages displaying different compounds with the cell and identifying at
4 least one replicable genetic package displaying a compound that is transported into or through
5 the cell.

1 121. The method of claim 118, wherein the desired property is capacity to
2 be a substrate or inhibitor of an enzyme and the assaying step comprises contacting the
3 plurality of replicable genetic packages with the enzyme and identifying at least one
4 replicable genetic package displaying a compound that is a substrate or an inhibitor of the
5 enzyme.

1 122. A method of screening a library of compounds, comprising:

2 (a) providing a plurality of different replicable genetic packages each
3 displaying a compound other than an expressed polypeptide, and harboring a heterologous
4 nucleic acid tag;

5 (b) assaying the plurality of replicable genetic packages to identify at least
6 one replicable genetic package displaying at least one compound with a desired property; and

7 (c) decoding the heterologous nucleic acid tag of the at least one replicable
8 genetic package to identify a characteristic of the at least one compound with the desirable
9 property.

1 123. The method of claim 122, wherein a plurality of replicable genetic
2 packages are combined into a pool and the pool contacted with a compound, the replicable
3 genetic packages harboring different heterologous nucleic acid tags, whereby replicable
4 genetic packages harboring different tags bear the same compound.

1 124. The method of claim 122, wherein a plurality of compounds to be
2 screened are combined into a pool and a plurality of replicable genetic packages harboring
3 different nucleic acid tags are combined into a pool, and the pool of replicable genetic

4 packages is contacted with the pool of compounds, whereby replicable genetic packages
5 harboring different tags bear the same plurality of compounds.

1 125. A method of screening a library of compounds, comprising:

(a) for each compound to be screened, contacting the compound with a replicable genetic package to form a plurality of replicable genetic packages displaying different compounds; and

1 126. The method of claim 125, wherein different replicable genetic
2 packages harbor different heterologous nucleic acid tags, and the method further comprises
3 decoding the heterologous nucleic acid tag of the at least one replicable genetic package to
4 identify a characteristic of the at least one compound with the desirable property.